

5 WHAT IS CLAIMED IS:

1. A method for treating cancer in a mammal in need thereof which comprises administering to said mammal amounts of a selective inhibitor of the activity of one or more of the isoforms of Akt.

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2. The method according to Claim 1 wherein the selective inhibitor is a small organic molecule.

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3. The method according to Claim 1 wherein the selective inhibitor inhibits the phosphorylation of one or more of the isoforms of Akt by upstream kinases and inhibits the phosphorylation of protein targets of an isoform or isoforms of Akt by the activated isoform or isoforms of Akt.

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4. The method according to Claim 1 wherein the selective inhibitor inhibits the phosphorylation of one or more of the isoforms of Akt by upstream kinases or inhibits the phosphorylation of protein targets of an isoform or isoforms of Akt by the activated isoform or isoforms of Akt.

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5. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt1.

6. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt2.

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7. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt1 and Akt2.

8. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt1 and Akt3.

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9. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt2 and Akt3.

5                   10.    The method according to Claim 2 wherein the inhibitor is a selective inhibitor of the activity of Akt3.

10                   11.    A method for treating cancer in a mammal in need thereof which comprises administering to said mammal amounts of an inhibitor of the activity of one or more of the isoforms of Akt wherein the inhibition by the inhibitor is dependent on the presence of the pleckstrin homology domain of the isoforms of Akt.

15                   12.    The method according to Claim 11 wherein the inhibitor is a selective inhibitor of the activity of Akt1.

                  13.    The method according to Claim 11 wherein the inhibitor is a selective inhibitor of the activity of Akt2.

20                   14.    The method according to Claim 11 wherein the inhibitor is a selective inhibitor of the activity of Akt3.

                  15.    The method according to Claim 11 wherein the inhibitor is a selective inhibitor of Akt1 and Akt2.

25                   16.    The method according to Claim 11 wherein the inhibitor is a selective inhibitor of Akt1 and Akt3.

30                   17.    The method according to Claim 11 wherein the inhibitor is a selective inhibitor of Akt2 and Akt3.

                  18.    The method according to Claim 11 wherein the inhibitor is a selective inhibitor of Akt1, Akt2 and Akt3.

35                   19.    A method for treating cancer in a mammal in need thereof which comprises administering to said mammal amounts of an inhibitor of the activity of one or more of the isoforms of Akt wherein the inhibition by the inhibitor is dependent on the presence of the hinge region of the isoforms of Akt.

- 5                   20.    The method according to Claim 19 wherein the inhibitor is a selective inhibitor of the activity of Akt1.
21.    The method according to Claim 19 wherein the inhibitor is a selective inhibitor of the activity of Akt2.
- 10                  22.    The method according to Claim 19 wherein the inhibitor is a selective inhibitor of the activity of Akt3.
23.    The method according to Claim 19 wherein the inhibitor is a selective inhibitor of Akt1 and Akt2.
- 15                  24.    The method according to Claim 19 wherein the inhibitor is a selective inhibitor of Akt1 and Akt3.
25.    The method according to Claim 19 wherein the inhibitor is a selective inhibitor of Akt2 and Akt3.
- 20                  26.    The method according to Claim 19 wherein the inhibitor is a selective inhibitor of Akt1, Akt2 and Akt3.
27.    A method for treating cancer in a mammal in need thereof which comprises administering to said mammal amounts of an inhibitor of the activity of one or more of the isoforms of Akt wherein the inhibition by the inhibitor is dependent on the presence of the pleckstrin homology domain and the hinge region of the isoforms of Akt.
- 25                  28.    The method according to Claim 27 wherein the inhibitor is a selective inhibitor of the activity of Akt1.
29.    The method according to Claim 27 wherein the inhibitor is a selective inhibitor of the activity of Akt2.
- 30                  30.    The method according to Claim 27 wherein the inhibitor is a selective inhibitor of the activity of Akt3.
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31. The method according to Claim 27 wherein the inhibitor is a selective inhibitor of Akt1 and Akt2.

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32. The method according to Claim 27 wherein the inhibitor is a selective inhibitor of Akt1 and Akt3.

33. The method according to Claim 27 wherein the inhibitor is a selective inhibitor of Akt2 and Akt3.

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34. The method according to Claim 27 wherein the inhibitor is a selective inhibitor of Akt1, Akt2 and Akt3.

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35. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt1, but is not an inhibitor of the activity of a modified Akt1 that lacks the pleckstrin homology domain.

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36. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt2, but is not an inhibitor of the activity of a modified Akt2 that lacks the pleckstrin homology domain.

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37. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt3, but is not an inhibitor of the activity of a modified Akt3 that lacks the pleckstrin homology domain.

38. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt1 and Akt2, but is not an inhibitor of the activity of a modified Akt1 that lacks the pleckstrin homology domain, a modified Akt2 that lacks the pleckstrin homology domain or both a modified Akt1 and a modified Akt2 protein that lack their pleckstrin homology domains.

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39. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt1 and Akt3, but is not an inhibitor of the activity of a modified Akt1 that lacks the pleckstrin homology domain, a modified

- 5 Akt3 that lacks the pleckstrin homology domain or both a modified Akt1 and a modified Akt3 protein that lack their pleckstrin homology domains.

40. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt2 and Akt3, but is not an inhibitor of the activity of a modified Akt2 that lacks the pleckstrin homology domain, a modified Akt3 that lacks the pleckstrin homology domain or both a modified Akt2 and a modified Akt3 protein that lack their pleckstrin homology domains.

41. The method according to Claim 1 wherein the inhibitor is a selective inhibitor of the activity of Akt1, Akt2 and Akt3, but is not an inhibitor of the activity of a modified Akt1 that lacks the pleckstrin homology domain, a modified Akt2 that lacks the pleckstrin homology domain, a modified Akt3 that lacks the pleckstrin homology domain or two or three modified Akt isoforms that lack their pleckstrin homology domains.

42. A method for identifying a compound that is a selective inhibitor of one, two or three of the Akt isoforms, whose inhibitory efficacy is dependent on the pleckstrin homology domain, that comprises the steps of:

- a) determining the efficacy of a test compound in inhibiting the activity of an Akt isoform;
- b) determining the efficacy of the test compound in inhibiting the activity of the Akt isoform that has been modified to delete the pleckstrin homology domain; and
- c) comparing the activity of the test compound against the Akt isoform with the activity of the test compound against the modified Akt isoform lacking the pleckstrin homology domain.

43. A method for identifying a compound that is a selective inhibitor of one, two or three of the Akt isoforms, whose inhibitory efficacy is dependent on the hinge region of Akt, that comprises the steps of:

- a) determining the efficacy of a test compound in inhibiting the activity of an Akt isoform;

- 5           b) determining the efficacy of the test compound in inhibiting the activity  
of the Akt isoform that has been modified to delete the pleckstrin  
homology domain;
- c) determining the efficacy of the test compound in inhibiting the activity  
of the Akt isoform that has been modified to delete the pleckstrin  
10          homology domain and the hinge region; and
- d) comparing the activity of the test compound against the Akt isoform,  
the activity of the test compound against the modified Akt isoform  
lacking the PH domain, and the activity of the test compound against  
the modified Akt isoform lacking the pleckstrin homology domain and  
15          the hinge region.

          44.    A modified Akt isoform lacking only the pleckstrin  
homology domain.

20           45.    A modified Akt isoform lacking only the hinge region.

          46.    A modified Akt isoform lacking the full pleckstrin  
homology domain and the full hinge region.

25           47.    A method of treating or preventing cancer which comprises  
administering a selective inhibitor of Akt in combination with a second compound  
selected from:

- 1)    an estrogen receptor modulator,  
          2)    an androgen receptor modulator,  
30          3)    a retinoid receptor modulator,  
          4)    a cytotoxic/cytostatic agent,  
          5)    an antiproliferative agent,  
          6)    a prenyl-protein transferase inhibitor,  
          7)    an HMG-CoA reductase inhibitor,  
35          8)    an HIV protease inhibitor,  
          9)    a reverse transcriptase inhibitor,  
          10)   an angiogenesis inhibitor,  
          11)   PPAR- $\gamma$  agonists,  
          12)   PPAR- $\delta$  agonists,

- 5                   13)    an inhibitor of inherent multidrug resistance,  
                  14)    an anti-emetic agent,  
                  15)    an agent useful in the treatment of anemia,  
                  16)    an agent useful in the treatment of neutropenia,  
                  17)    an immunologic-enhancing drug,  
10               18)    an inhibitor of cell proliferation and survival signaling, and  
                  19)    an agent that interferes with a cell cycle checkpoint.

                  48.    A method according to Claim 47 wherein the second  
compound is a cytotoxic/cytostatic agent which is an inhibitor of kinases involved in  
15   mitotic progression.

                  49.    The method according to Claim 47 wherein the selective  
inhibitor of Akt is a selective inhibitor of Akt1.

20               50.    The method according to Claim 47 wherein the selective  
inhibitor of Akt is a selective inhibitor of Akt2.

                  51.    The method according to Claim 47 wherein the selective  
inhibitor of Akt is a selective inhibitor of both Akt1 and Akt2.

25               52.    A method of treating cancer which comprises administering a  
therapeutically effective amount of a selective inhibitor of Akt in combination with  
radiation therapy and a second compound selected from:

- 1)    an estrogen receptor modulator,  
30               2)    an androgen receptor modulator,  
                  3)    a retinoid receptor modulator,  
                  4)    a cytotoxic/cytostatic agent,  
                  5)    an antiproliferative agent,  
                  6)    a prenyl-protein transferase inhibitor,  
35               7)    an HMG-CoA reductase inhibitor,  
                  8)    an HIV protease inhibitor,  
                  9)    a reverse transcriptase inhibitor,  
                  10)   an angiogenesis inhibitor,  
                  11)   PPAR- $\gamma$  agonists,

- 5                   12)    PPAR- $\delta$  agonists,  
                  13)    an inhibitor of inherent multidrug resistance,  
                  14)    an anti-emetic agent,  
                  15)    an agent useful in the treatment of anemia,  
                  16)    an agent useful in the treatment of neutropenia,  
10               17)    an immunologic-enhancing drug,  
                  18)    an inhibitor of cell proliferation and survival signaling, and  
                  19)    an agent that interferes with a cell cycle checkpoint.

                  53.    The method according to Claim 52 wherein the selective  
15   inhibitor of Akt is a selective inhibitor of Akt1.

                  54.    The method according to Claim 52 wherein the selective  
inhibitor of Akt is a selective inhibitor of Akt2.

20               55.    The method according to Claim 52 wherein the selective  
inhibitor of Akt is a selective inhibitor of both Akt1 and Akt2.